Remarks

Applicants have cancelled claims 25-28 from the present invention in response to the Examiner's withdrawal of the claims from further consideration following Applicants' election to the Restriction Requirement. However, cancellation of the claims is without prejudice to Applicants' ability to prosecute those claims in a future continuation application. Thus, the cancellation only relates to claims 25-28 in the present application and only affects the prosecution of the presently elected claims.

Applicants have also made corrections to the specification to address informalities. The Examiner is thanked for pointing them out. Applicants have further amended the claims to more clearly define Applicants' invention. Support for discussion of imaging during a held breath or in a sealed lung in a non-breathing subject is found in Applicants' specification at least in the discussion on page 5, measuring local concentrations of the hyperpolarized noble gas is also found at least at page 5, while the use of scale-based fuzzy connectedness is found at least at page 7. No new matter has been added.

Applicants also appreciate the Examiner's indication that claims 4-6, 10-13 and 17-20 would be allowable if rewritten to include all of the limitations of the base independent claim and any intervening claims.

Response

Response to the rejections under 35 USC § 102(b)

The Examiner has rejected claims 1-2, 7, 8, 14, 15 and 21-24 under 35 USC § 102(b) as being anticipated by the disclosure of Kauczor *et al.* (1997) of 3-D imaging of lungs using hyperpolarized helium gas. The Examiner has also rejected claims 1-3, 7-9, 14-16, 21, 23 and 24 under 35 USC § 102(b) as being anticipated by the disclosure of Black *et al.*, (1996) which also performs 3-D imaging of lungs using hyperpolarized helium gas. According to the Examiner, in both cases, because MRI was used to assess pulmonary ventilation and its abnormalities, one would understand that either Kauczor *et al.* or Black *et al.* could also be used in the methods taught by applicants, for "imaging pulmonary compliance and distribution of functional residual

capacity." However, for the following reasons, Applicants traverse the arguments and the rejections.

As pointed out by Applicants in the Background section of the specification, it is well known that "[T]he use of hyperpolarized noble gases, such as ^{3}He, has been demonstrated to be useful in the imaging of gas distribution (ventilation) in the human lung" as referenced by Kauczor *et al.* and Black *et al.* However, as further explained in the Background section, "what has not been available until the present invention, has been a method for high resolution imaging of the gas spaces in the lung, with very high contrast between the signal intensity for the gas phase compared to the tissue phase, which would permit the combined imaging of FRC distribution and lung compliance."

The present invention offers novel equilibration methods for imaging lung compliance and distribution of functional residual capacity (FRC) in the lung using hyperpolarized helium-3 (^{3}He) gas (H^{3}He). The imaging of pulmonary compliance and measuring the distribution of FRC is accomplished in the present invention by, for the first time, adapting and extending known helium dilution principles and standard pulmonary function tests established for imaging the whole lung, to the imaging of *regional* lung volumes and compliance. By using hyperpolarized ^{3}He for *localized* imaging – as opposed to whole lung images as has been done in the prior art - the present method provides at least the following advantages over the prior art: (1) rapid imaging of FRC distribution; (2) true 3-dimensional imaging, and (3) very high resolution in the resulting image. None of these advantages are provided by either the cited Kauczor or Black references, each of which dates back to 1996 or 1997, before the present high resolution imaging technologies had been developed. In fact, contrary to the Examiner's conclusion, it would not have been possible for one of ordinary skill applying only the cited prior art methods of using MRI to assess pulmonary ventilation and its abnormalities to practice Applicants' methods for <u>local</u> imaging of pulmonary compliance and distribution of functional residual capacity, if for no other reason, because the imaging technologies were simply not yet available prior to 1998.

As pointed out in the Description of the Invention section of the specification, H^{3}He-based imaging is intrinsically faster and gives much higher resolution in 3-D than any prior method. In the present invention, as opposed to the cited prior art, MRI measures the local H^{3}He concentrations at high resolution, permitting measurement of volume in the whole lung, which was not previously possible based upon *local* measurements. Consequently, the use of local

measurement of H^3He to measure local lung volume produces entirely novel information, not previously found in the prior art. Applicants' claims are presently modified to reflect this novelty.

In practice in Applicants' invention, a known volume of H^3He is introduced into the sealed or fixed lung volume and the lung is imaged with a homogeneous coil, after which the lung images are divided into as many distinct voxels as the imaging resolution permits. The starting point for calculating local lung volume is the average signal intensity in each voxel divided by the signal intensity in the trachea in accordance with the formulas provided in the specification. The average concentration of H^3He in each voxel is calculated by dividing the amount of H^3He in each voxel divided by the volume of the voxel. The amount of H^3He in the voxel is simply calculated in terms of the concentration of H^3He in the gas space of the voxel multiplied by the volume of the gas space in the voxel. Consequently, as described, the average concentration of H^3He/voxel is provided by Applicants' Formula 1. Further, assuming that signal intensity is directly proportional to the concentration of H^3He, the gas volume/voxel is determined by Applicants' Formula 2. Local FRC is quite simply the ratio of signal intensity in the voxel divided by signal intensity in the trachea, multiplied by the volume of the voxel.

The lung volume was measured by segmenting the lung using scale-based fuzzy connectedness. Scale is a local morphometric parameter, defined at an image point *p* as the radius of the largest hyperball inside a homogenous region with center at *p* (see, Saha et al., Computer Vision and Image Understanding, 77:145-174 (2000)). A hard segmentation of the fuzzy lung image was obtained by using a optimal threshholding method (Udupa *et al.*, IEEE Transactions on Pattern Analysis and Machine Intelligence, 23:689-706 (2001)) that selected the threshold that best complied with object morphology. However, although not available at the 1996/97 publication date of the Kauczor or Black references, Applicants do not teach or claim scale based fuzzy connectedness per se. Rather, it is a tool used in the present invention, but not available prior to 1998, to generate ventilation images wherein high membership values are assigned to lung tissue regions, and low values to non-lung regions. See, *e.g.*, page 7. The optimum threshold selection method generated hard segmentations from the fuzzy lung images that were visually acceptable for all cases, permitting the lung volume to be calculated from each segmentation.

Notably, because the prior art offers no teaching that relates to *local* imaging FRC or compliance (including the cited prior art references), there are no existing standards available for direct comparison to the equilibration method. Thus, because the prior art, including Kauczor and Black, not only fails to suggest any means or method for collecting and/or analyzing Applicants' FRC imaging or compliance data based upon hard segmentation of the fuzzy lung image, there existed no known benchmark to validate Applicants' findings. Accordingly, as set forth in the Examples, they had to develop a system utilizing ^{4}He dilution techniques to validate measurements of *local* lung volumes (this is because known techniques are only taught for measuring *whole* lung volumes). This difference is one of the principles that distinguishes Applicants' method, and the data produced using the method, from any known prior art. Had Applicants' methods been known, validating standards would have been available to Applicants – but they were not.

Accordingly, since the cited references fall to teach every element of Applicants' claimed invention, Applicants respectfully request withdrawal of the 35 USC § 102(b) rejections of Applicants' patent application.

Response to the rejections under 35 USC § 103

The Examiner has rejected claim 22 under 35 USC § 103 as being obvious over the disclosure of Black *et al.*, (1996), which performs the above-discussed whole lung, 3-D imaging in mammals (guinea pigs) using hyperpolarized helium gas. The Examiner argues that the guinea pig lung functions are similar to that of a human, and therefore, the claim would have been obvious over the cited reference. However, for the above stated reasons, Black *et al.* fails to teach Applicants' method of the present invention. Therefore, it is irrelevant which lungs were evaluated, or in which species. Regardless of the species tested Black *et al.* used an entirely different imaging process to calculate pulmonary compliance and/or FRC distribution.

Since no reference is cited to fill-in the deficits of Black as to Applicants' invention, and the state of the art in 1997 could not provide the missing elements, the Examiner's rejection is misplaced. Black could neither anticipate, nor obviate any claim of Applicants' application. Accordingly, Applicants respectfully request withdrawal of the 35 USC § 103 rejection over Applicants' claim 22.

In sum, based on the foregoing remarks, Applicants respectfully seek removal of the rejections under 35 USC §102 and/ or under §103. All of Applicants' claims are now believed to be in condition for allowance. An early and favorable action toward that end is earnestly solicited.

Respectfully submitted,

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